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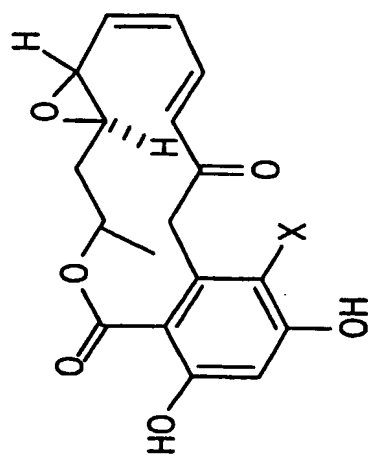
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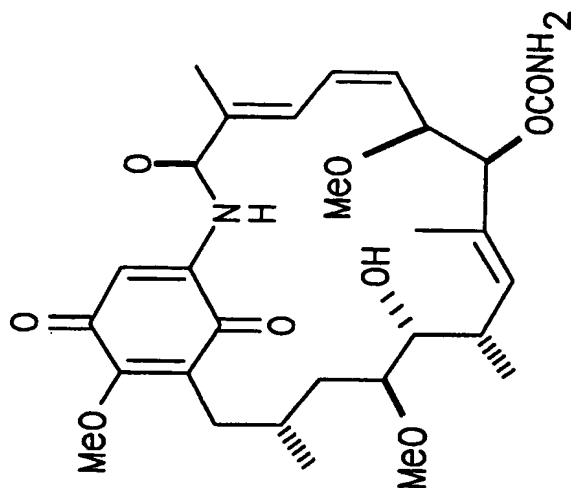
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FIG. 1



X=Cl Radical (1)

X=H Monocillin I (2)



Geldanamycin (3)

FIG.2

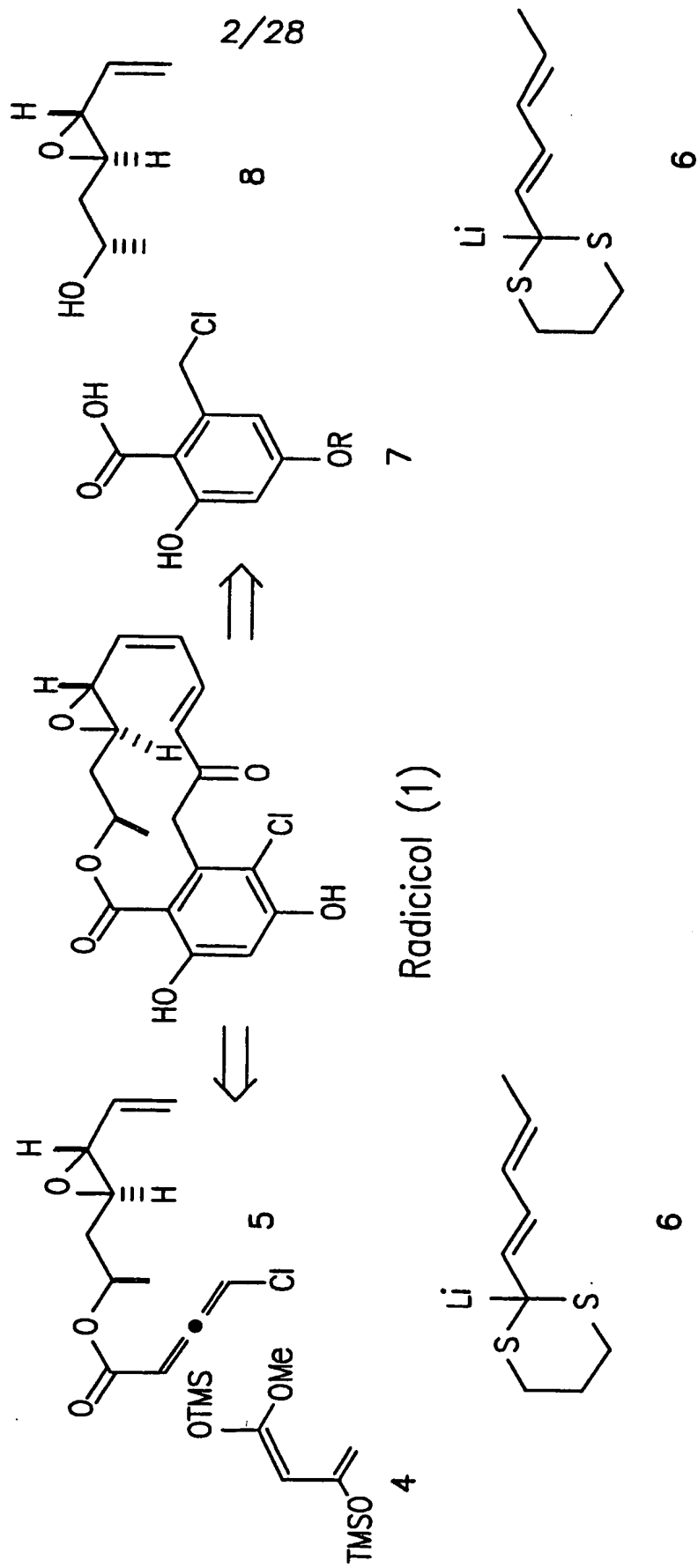
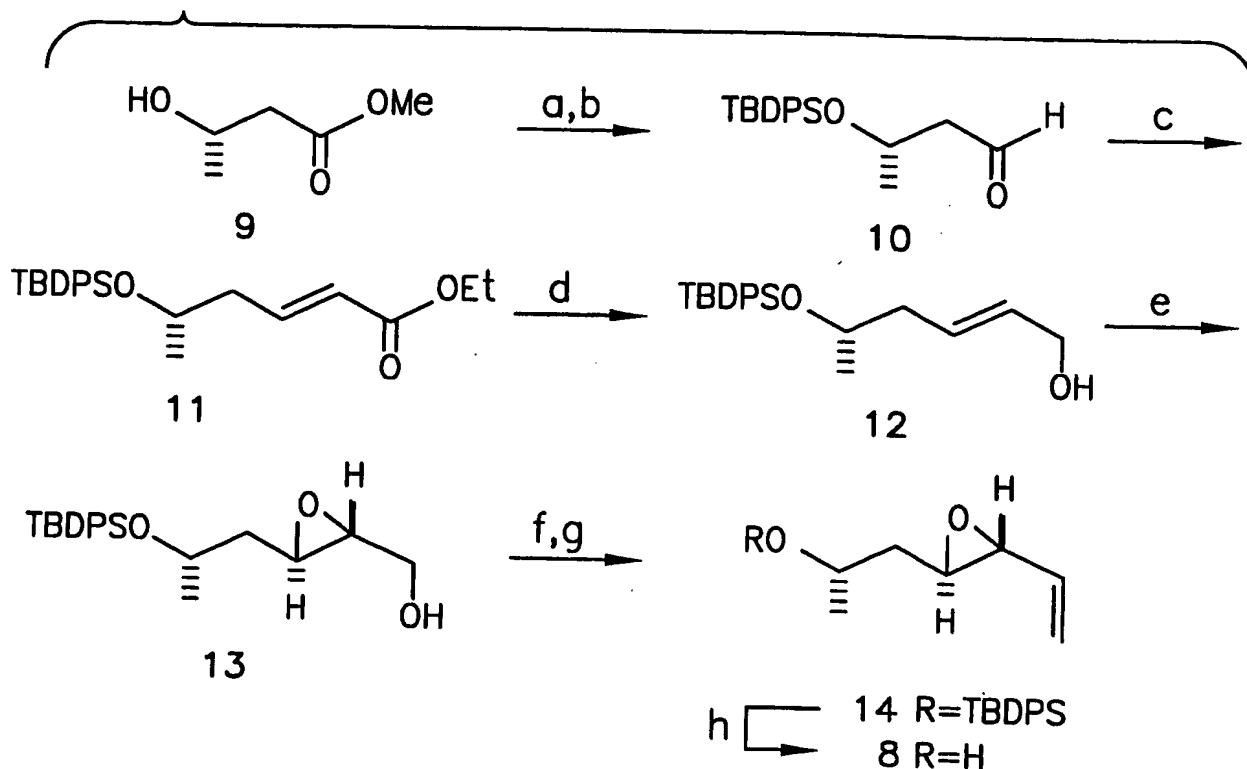


FIG.3

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- (a) TBDPSCI, imid., >95%; (b) DIBAL-H, -78 °C, 92%;  
 (c) LiCl, DIPEA (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, 95%;  
 (d) DIBAL-H, -20 °C, 96%; (e) (+)-DET, Ti(OiPr)<sub>4</sub>, TBHP, 90%, >95% ee; (f) SO<sub>3</sub>\*pyridine, Et<sub>3</sub>N, DMSO, 90%;  
 (g) PH<sub>3</sub>PCH<sub>3</sub>Br, NaHMDS, 0 °C, 82%; (h) TBAF, 89%.

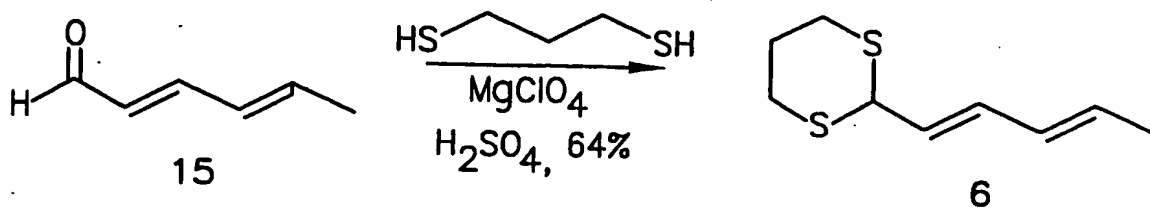
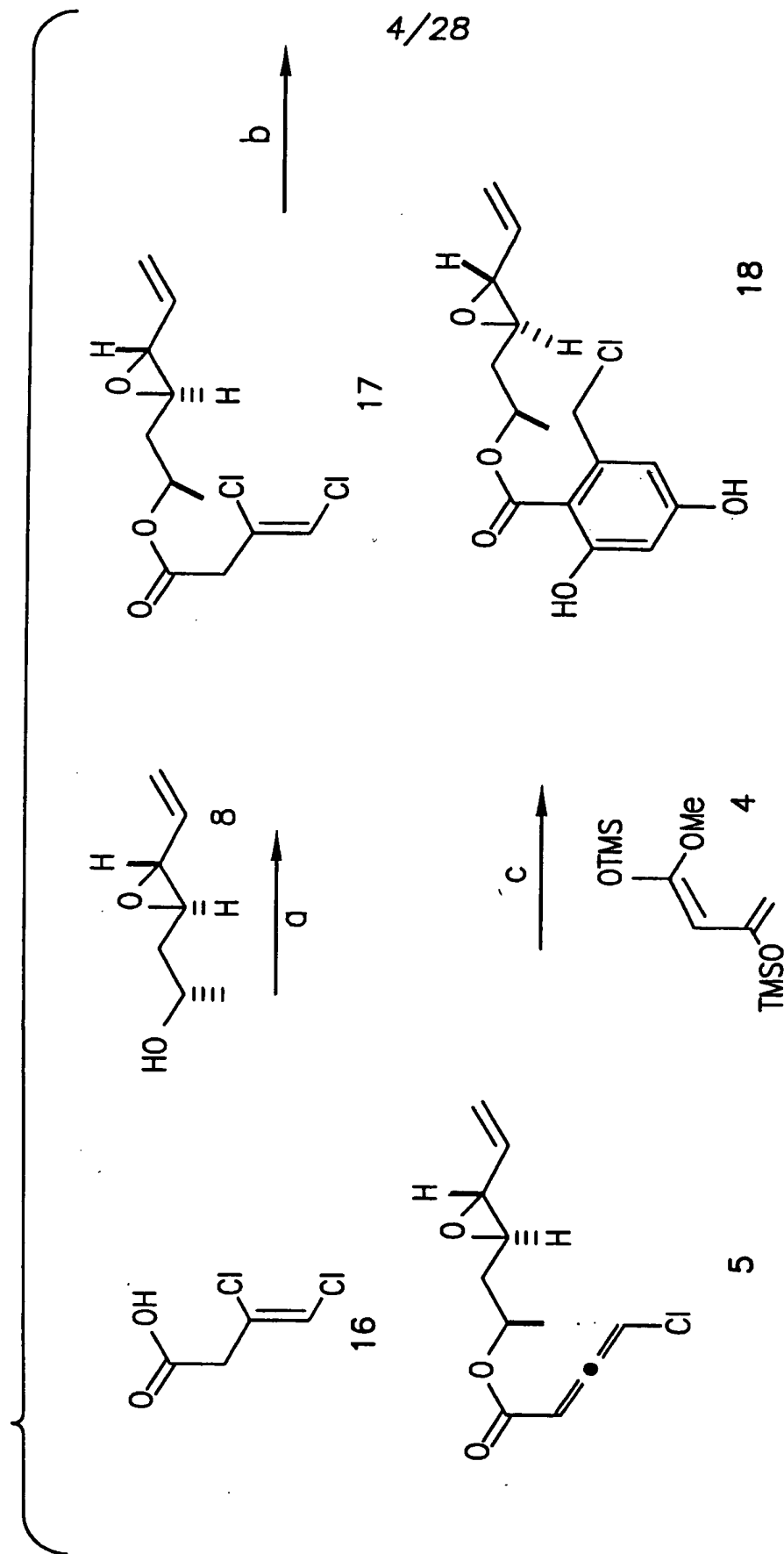


FIG.4



(a) DEAD, PPh<sub>3</sub>, 70%; (b.) iPr<sub>2</sub>NEt, 70%; (c.) 50% (4:1)

FIG. 5

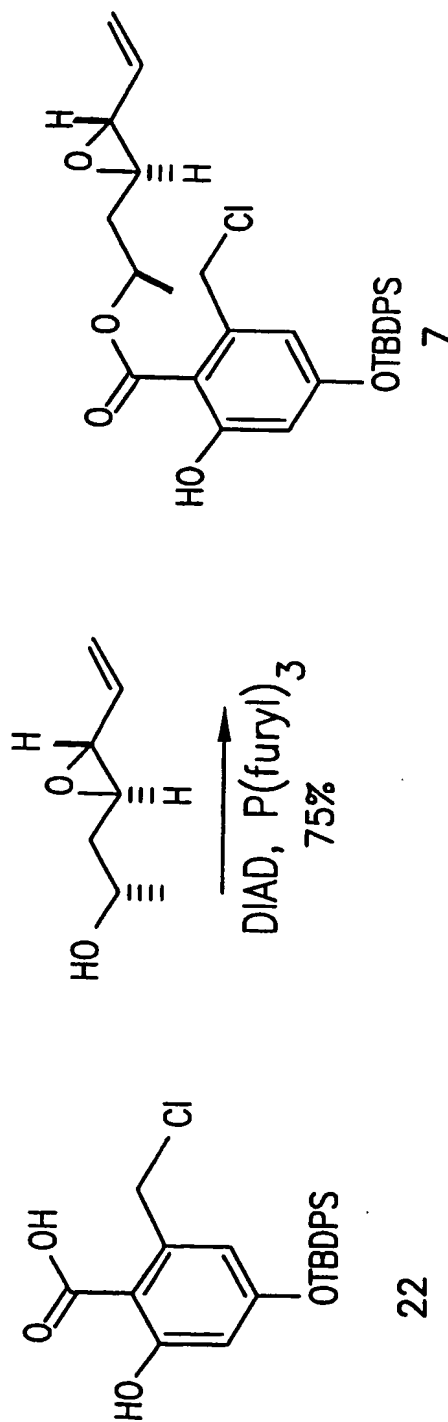
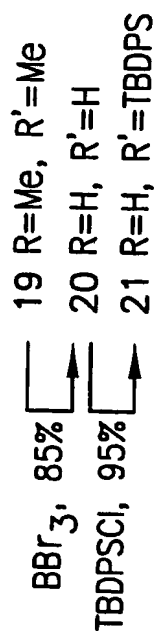
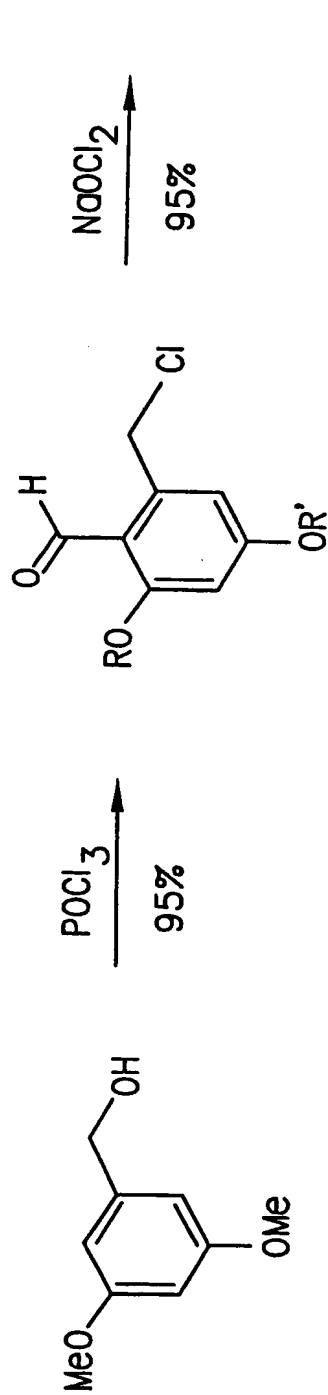
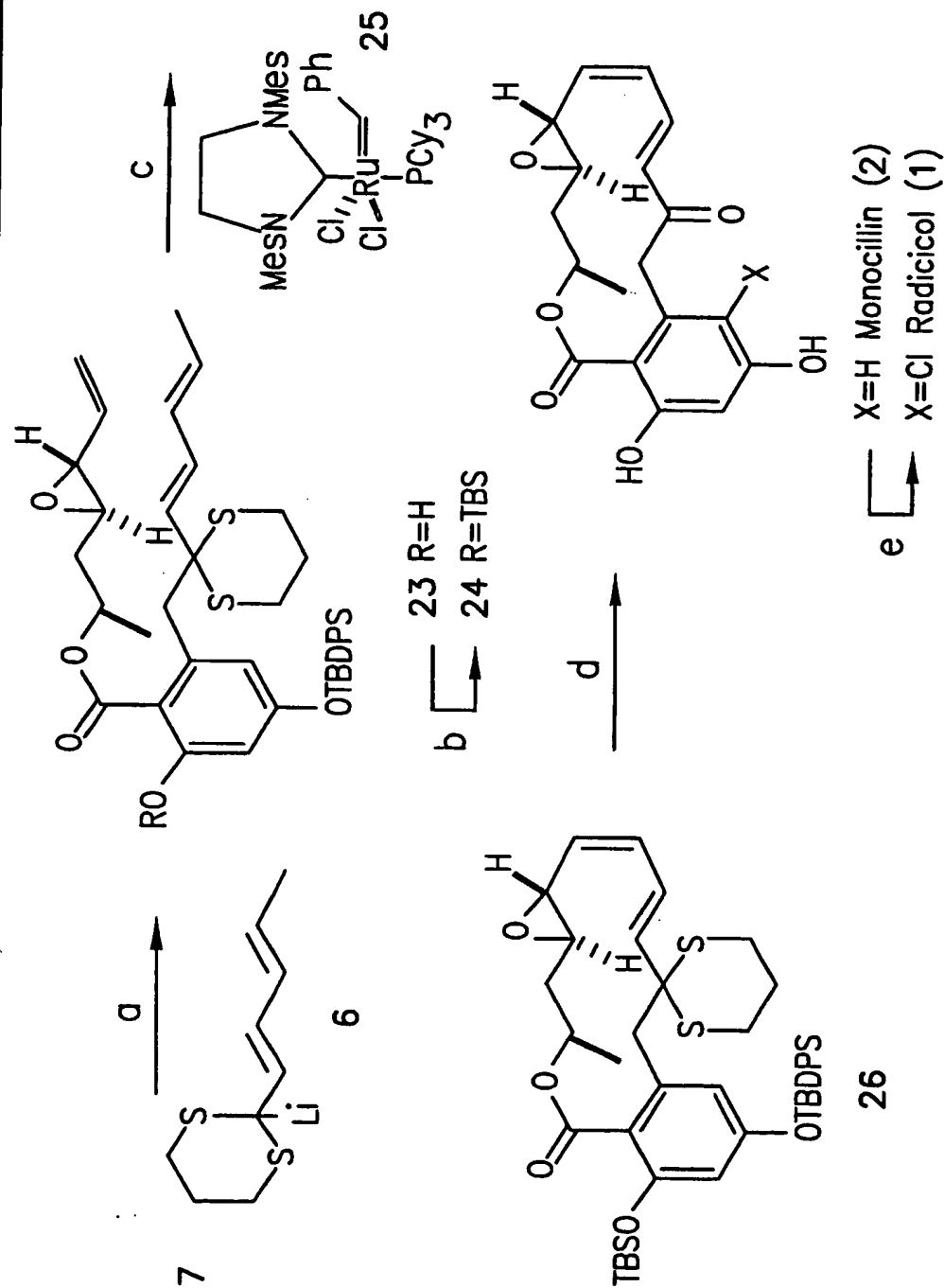


FIG. 6



a. *n*-BuLi,  $-78^{\circ}\text{C}$ , 50% (6:1); b. TBSCl, 83%; c. 42  $^{\circ}\text{C}$ , 70%; d. (i) mCPBA, (ii)  $\text{Ac}_2\text{O}$ ,  $\text{Et}_3\text{N}$ ,  $\text{H}_2\text{O}$ ,  $60^{\circ}\text{C}$ , (iii)  $\text{NaHCO}_3$ , MeOH, 60%; e.  $\text{SO}_2\text{Cl}_2$ , 50%

FIG. 7

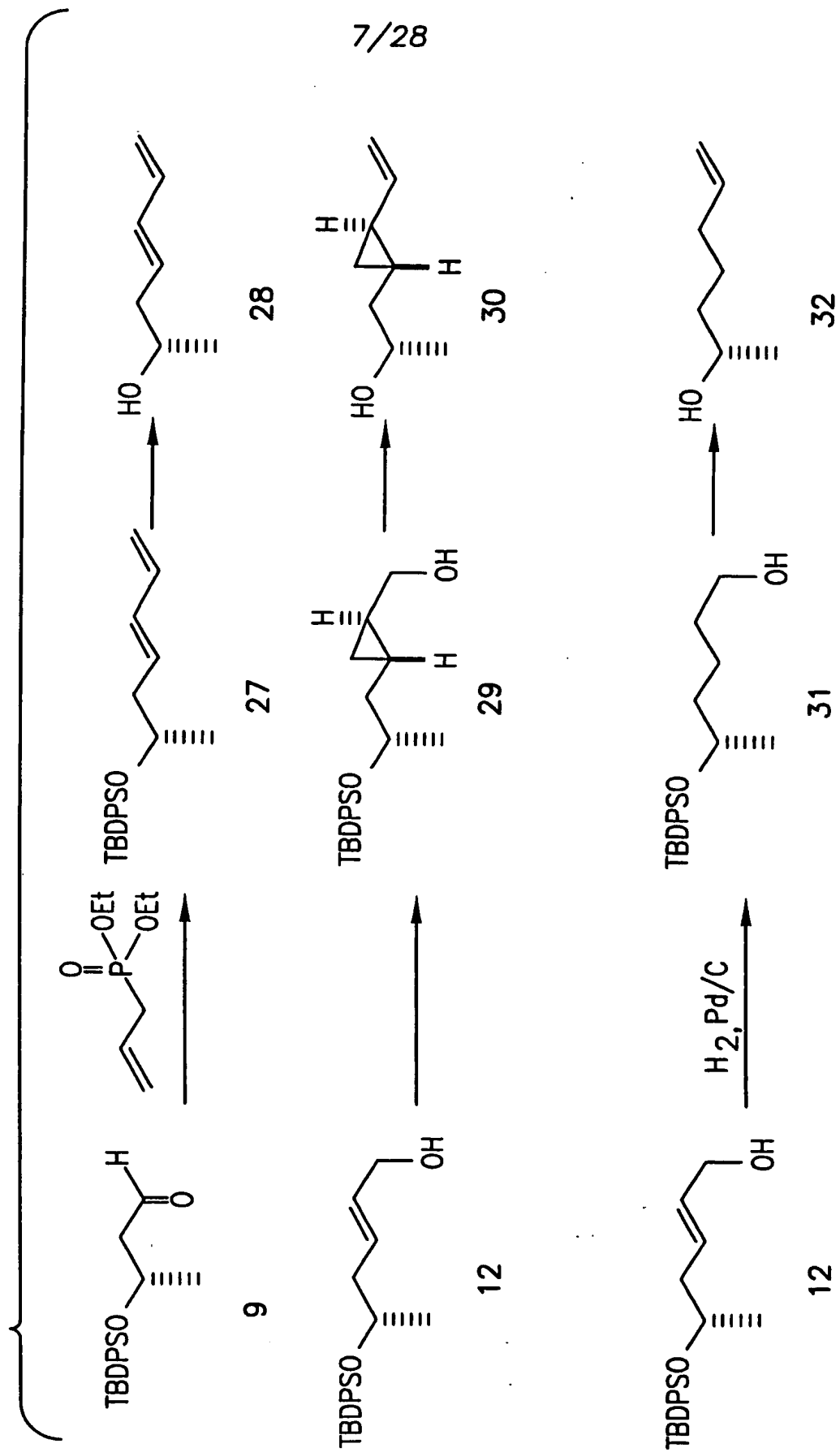




FIG. 8

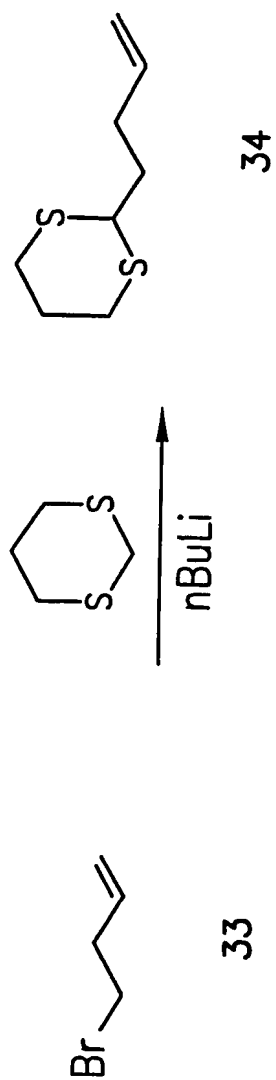


FIG. 9

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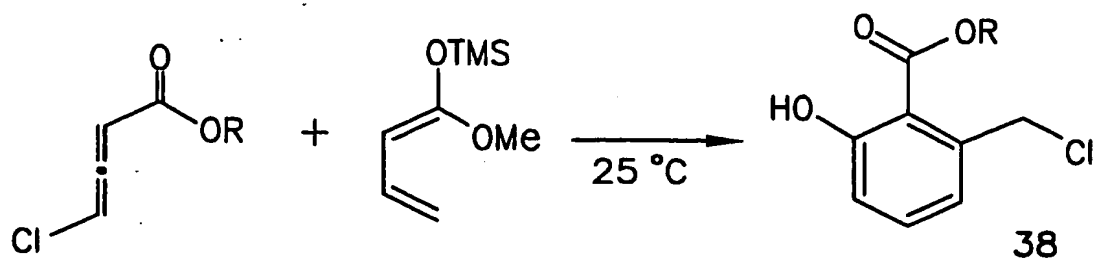
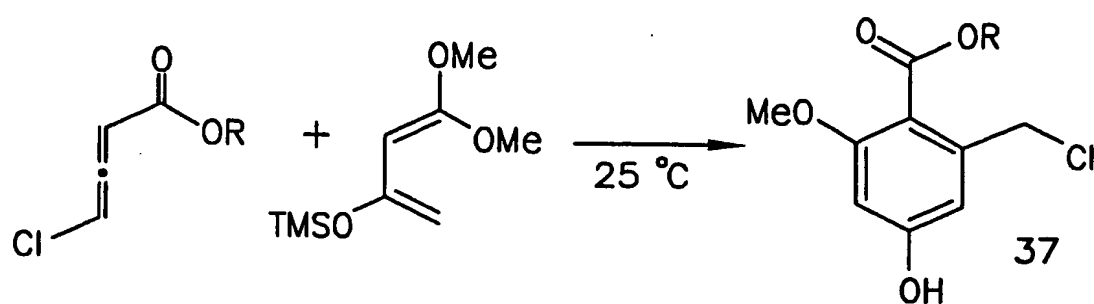
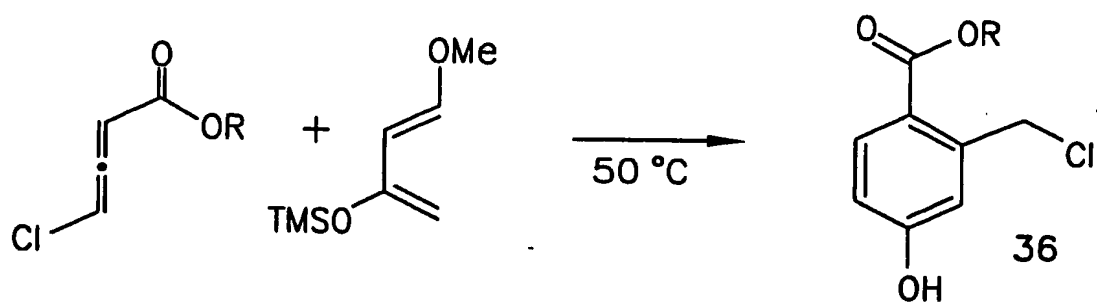
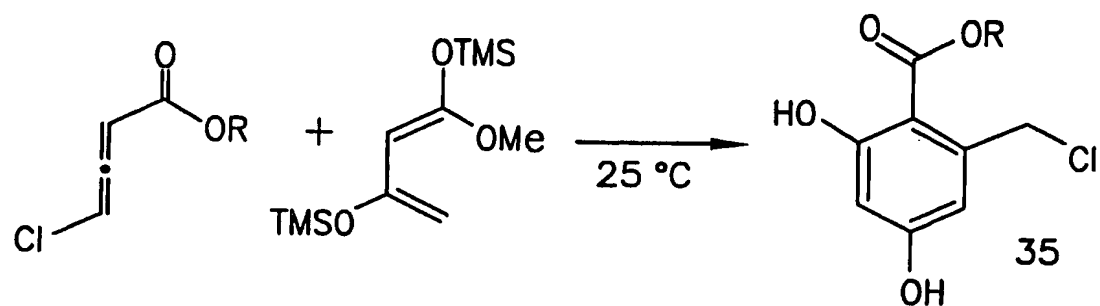
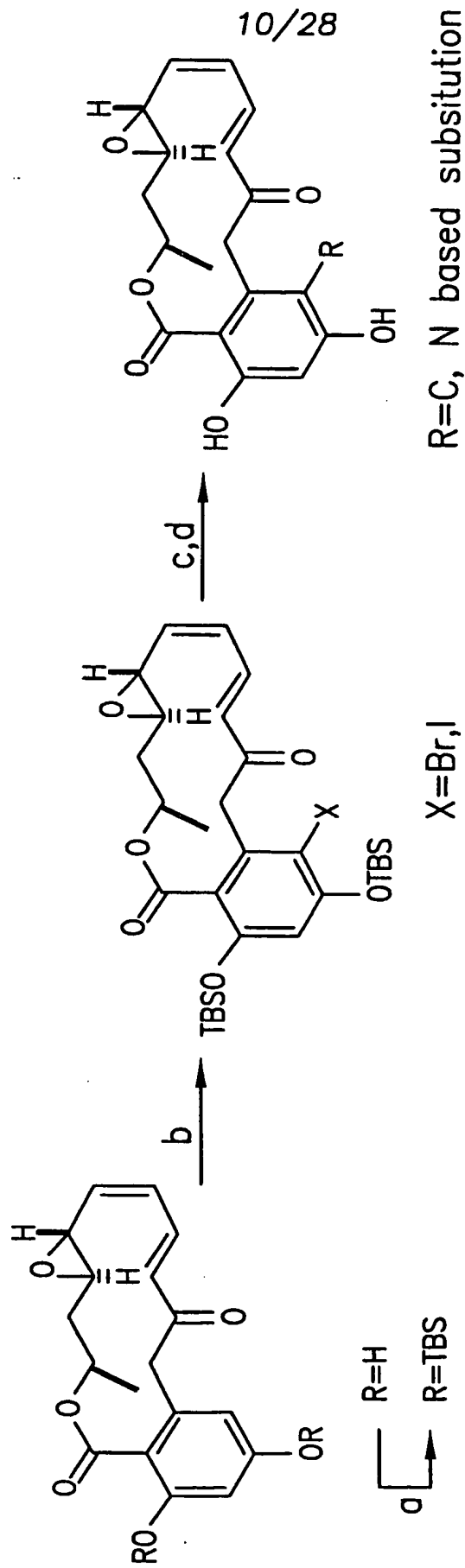
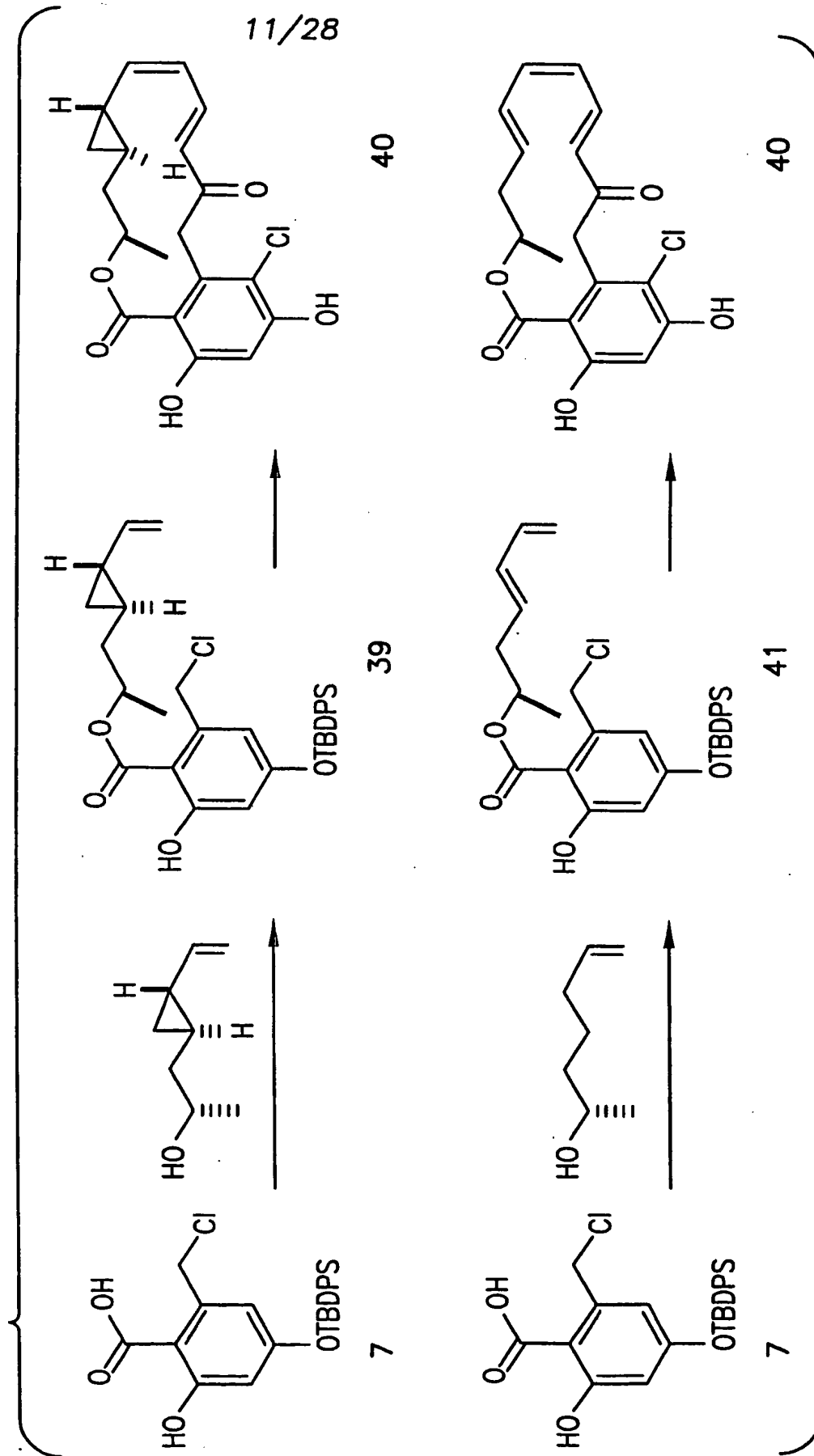


FIG.10



- a. TBSCl, pyridine; b. NIS or NBS, TsOH; c.  $Pd(PPh)_3$ ,  $RSnBu_3$ , d.  $nBu_4NF$

FIG. 11-1



TO FIG. 11-2

FROM FIG. 11-1

FIG. 11-2

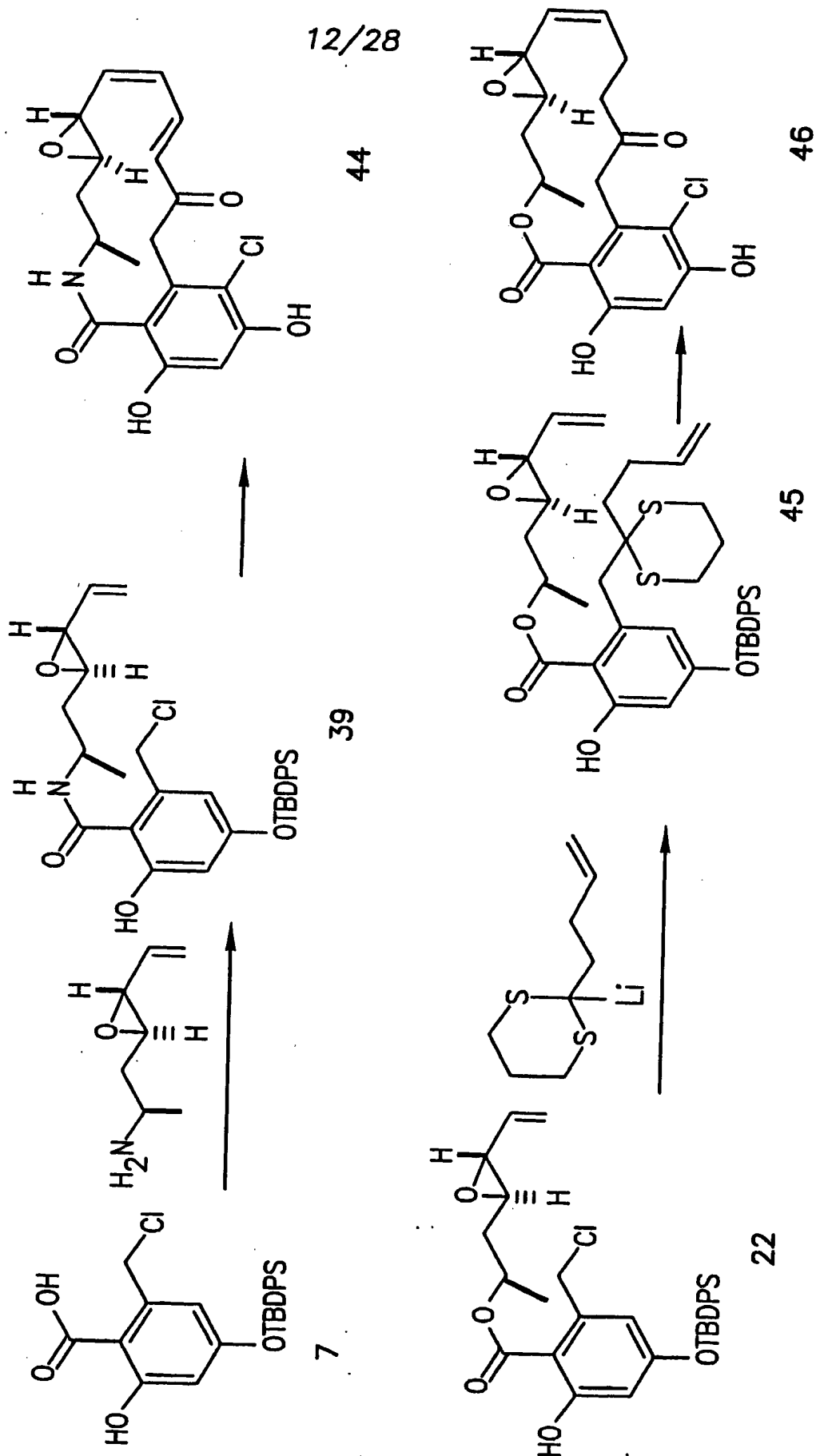
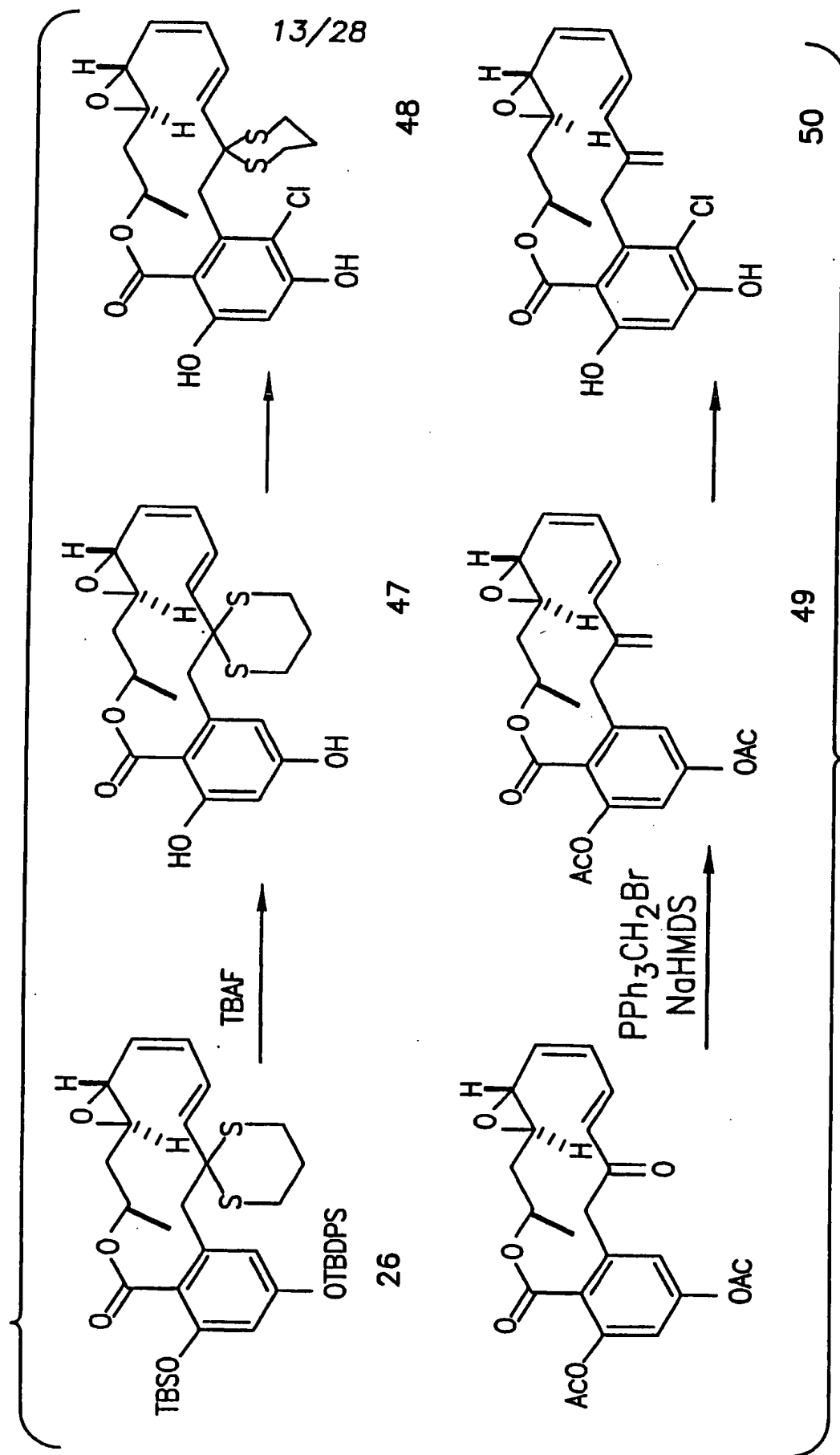


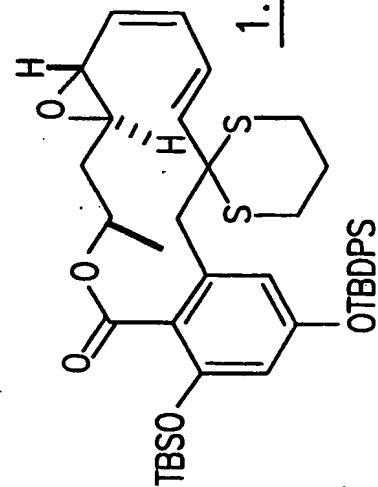
FIG. 12-1



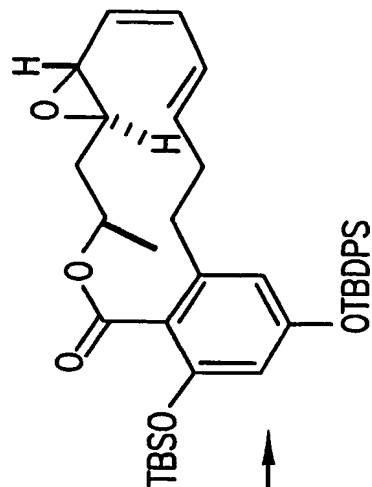
TO FIG. 12-2

FROM FIG. 12-1

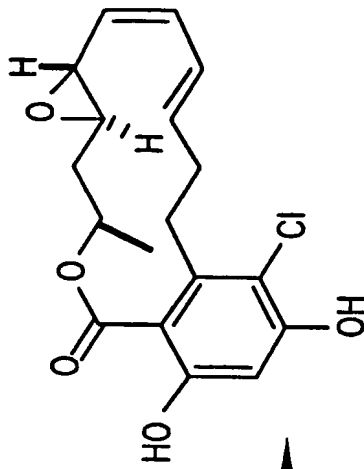
FIG. 12-2



1. Rainey Ni

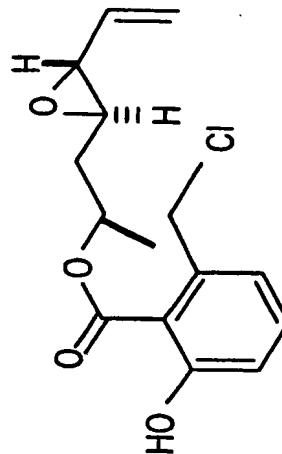
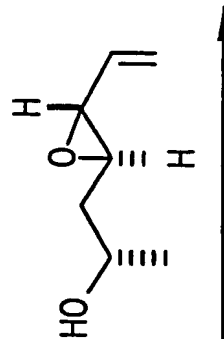
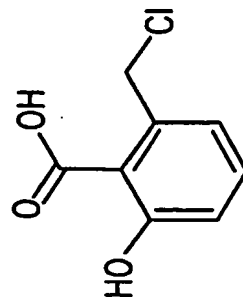


51

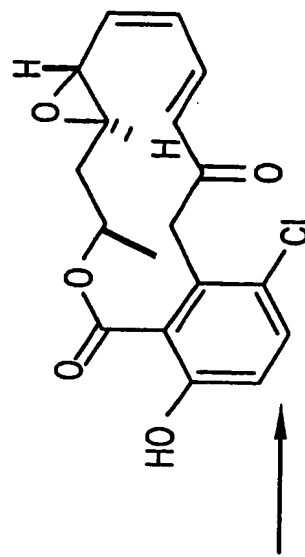


52

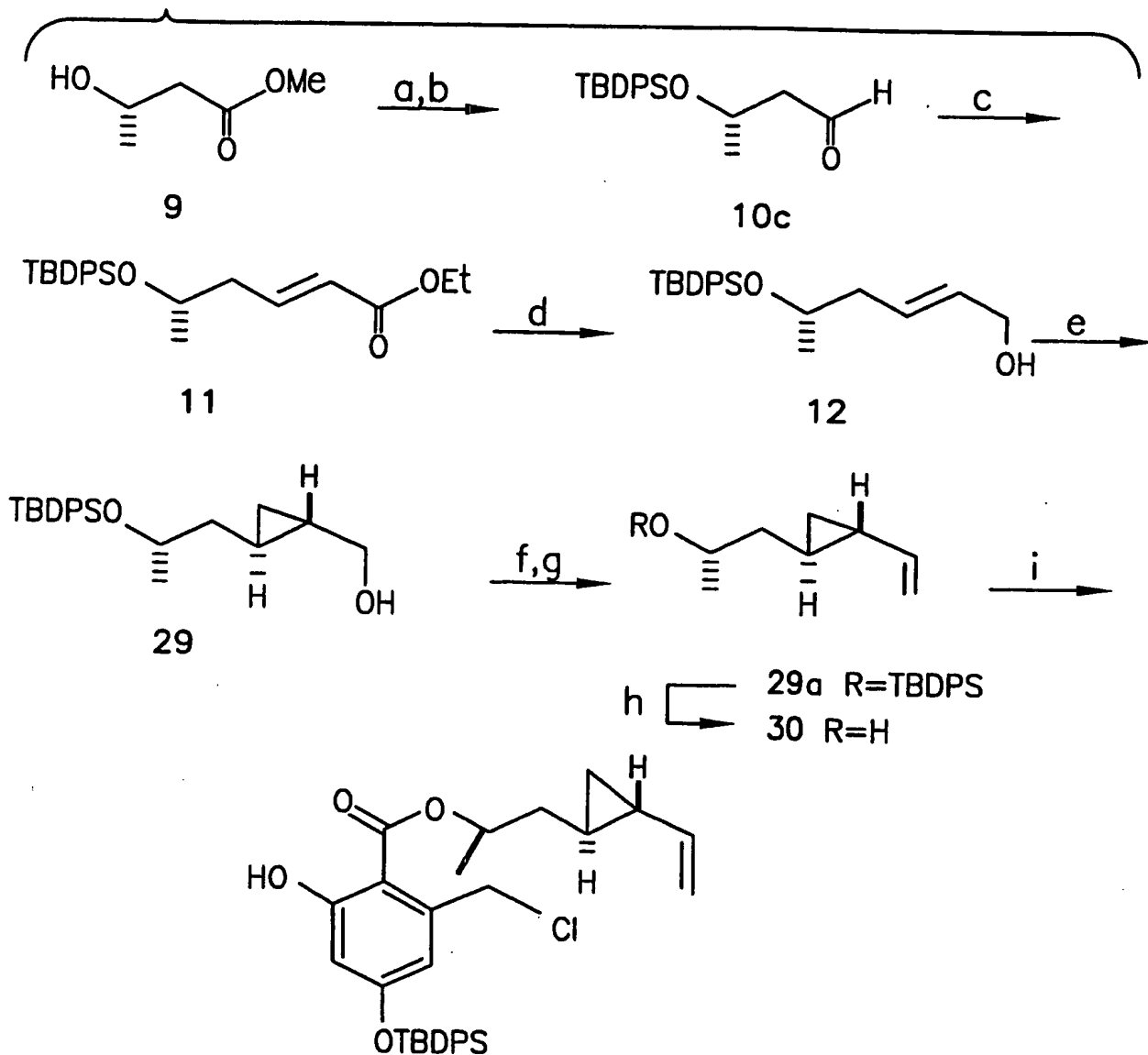
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53



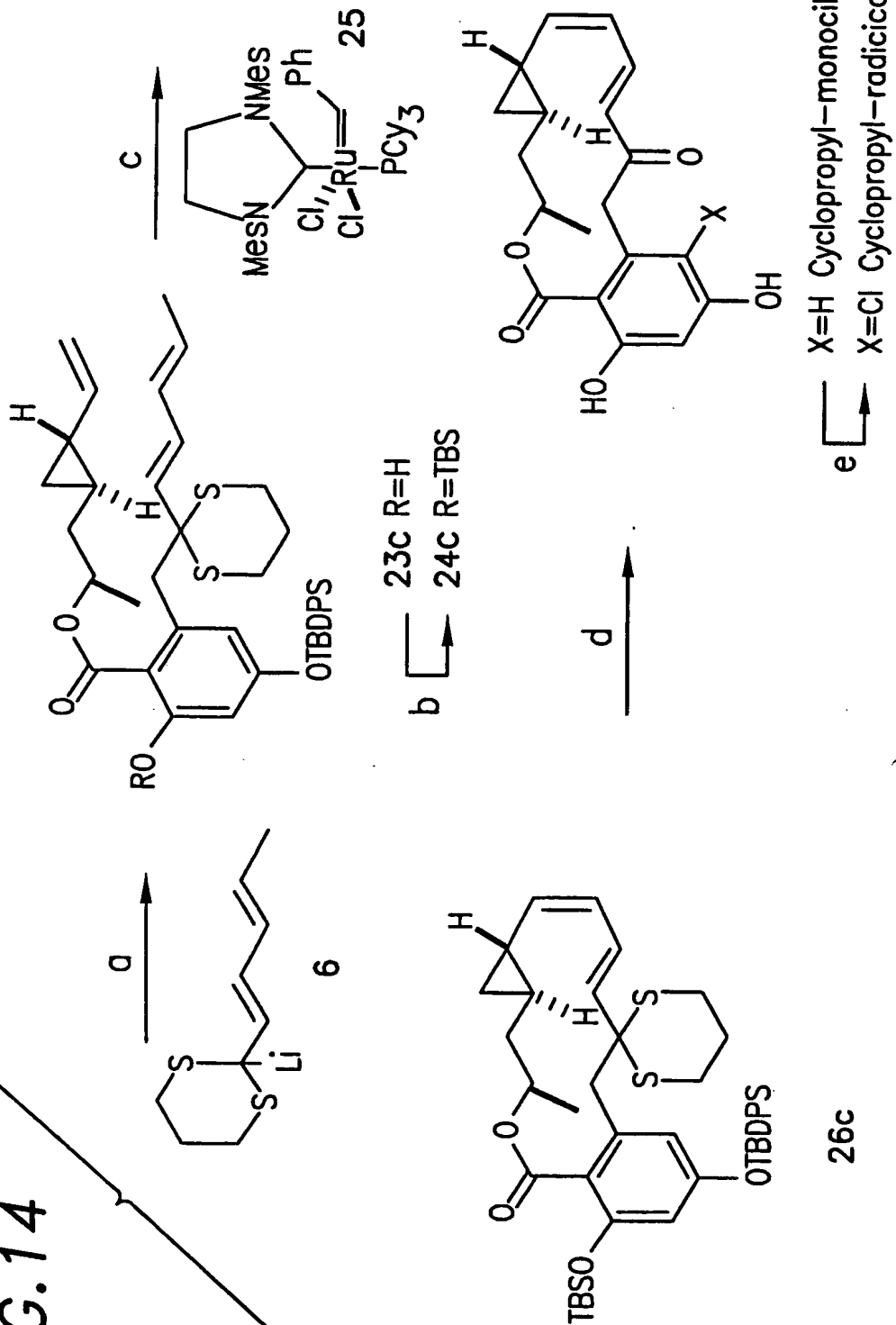
54



- <sup>a</sup> (a) TBDPSCl, imid., >95%; (b) DIBAL-H, -78 °C, 92%; (c) LiCl, DIPEA (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, 95%; (d) DIBAL-H -20 °C, 96%; (e) (+)-tetramethyltartaric acid diamide-BBu, Et<sub>2</sub>Zn, CH<sub>2</sub>I<sub>2</sub>, 9 >95% ee; (f) SO<sub>3</sub>\*pyridine, Et<sub>3</sub>N, DMSO, 90%; (g) Ph<sub>3</sub>PCH NaHMDS, 0 °C, 82%; (h) TBAF, 89%; (i) 7, P(furyl)<sub>3</sub>, DIA benzene, 60%

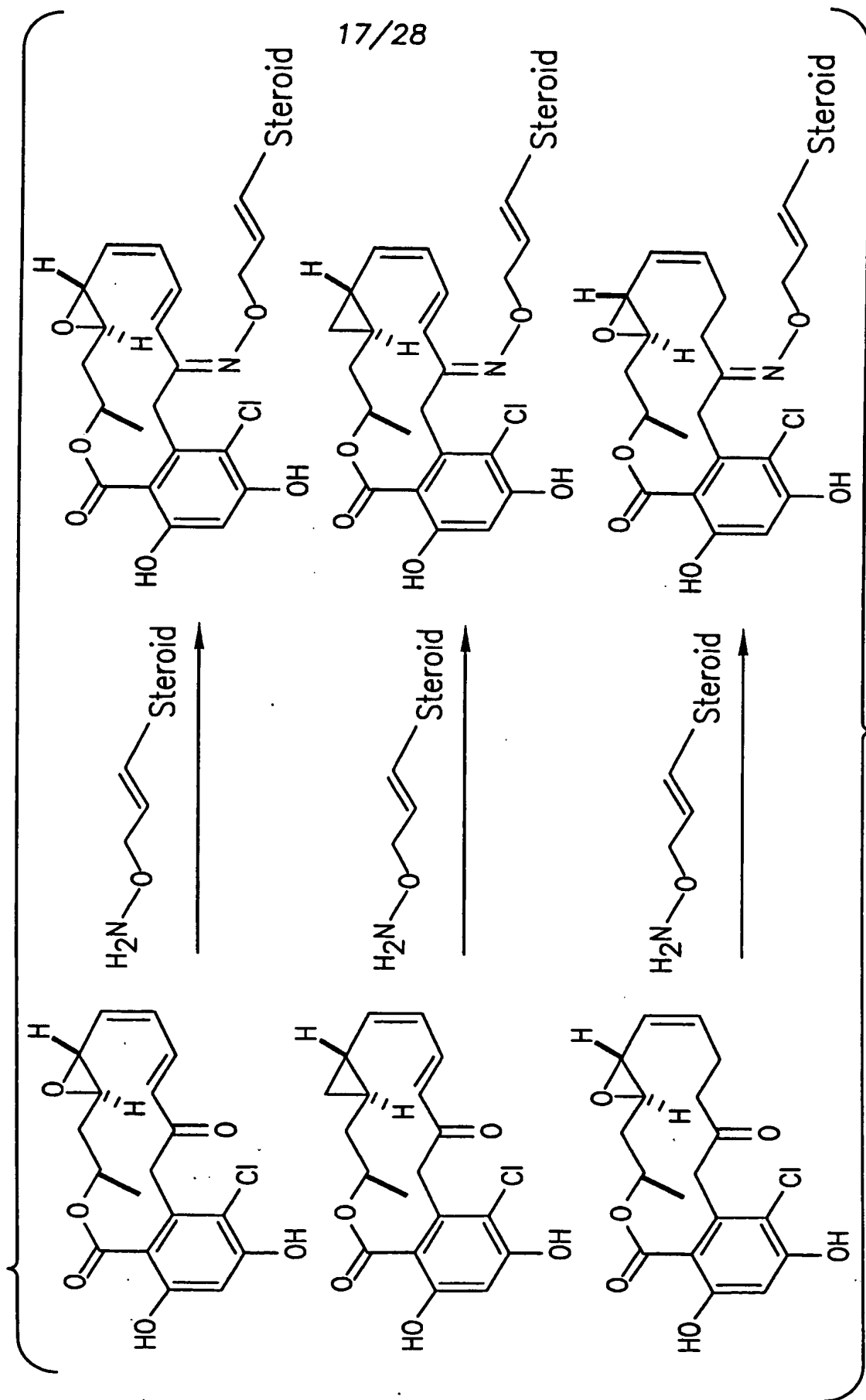


FIG. 14



a.  $n\text{-BuLi}$ ,  $-78^\circ\text{C}$ , 75% (3:1); b.  $\text{TBSCl}$ , 83%; c.  $42^\circ\text{C}$ , 20%; d. (i)  $\text{mCPBA}$ , (ii)  $\text{Ac}_2\text{O}$ ,  $\text{Et}_3\text{N}$ ,  $\text{H}_2\text{O}$ ,  $60^\circ\text{C}$ , (iii)  $\text{NaHCO}_3$ ,  $\text{MeOH}$ , 60%; e.  $\text{SO}_2\text{Cl}_2$ , 80%

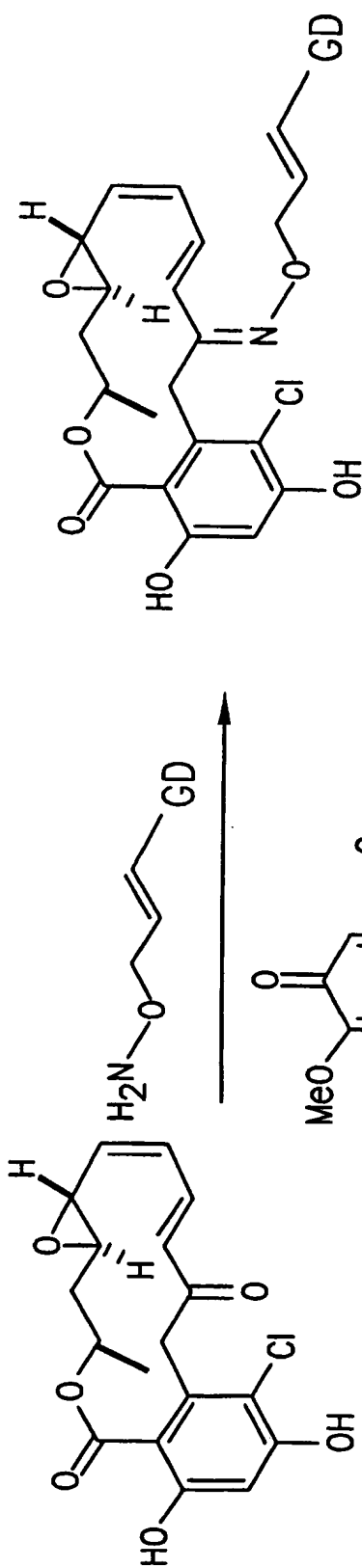
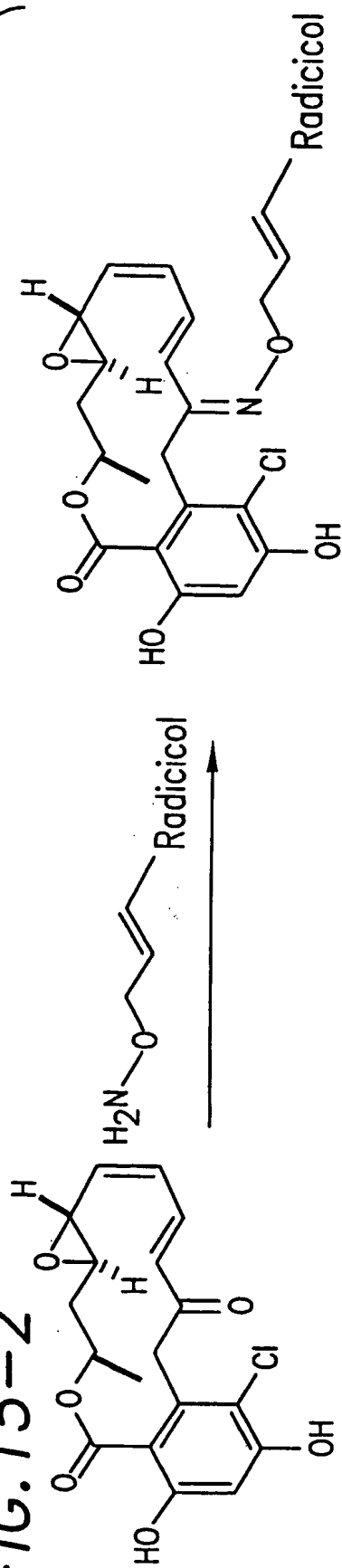
FIG. 15-1



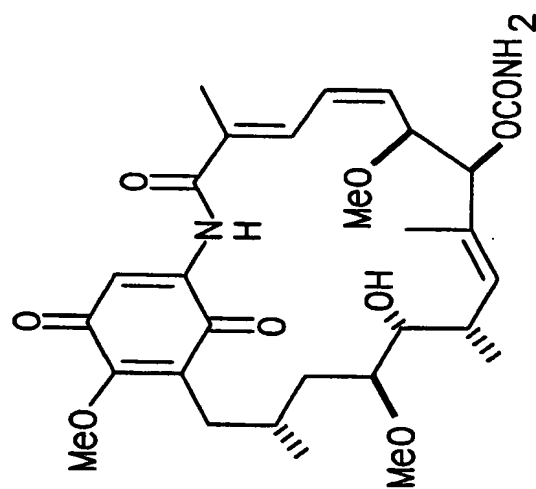
TO FIG. 15-2

FROM FIG. 15-1

FIG. 15-2

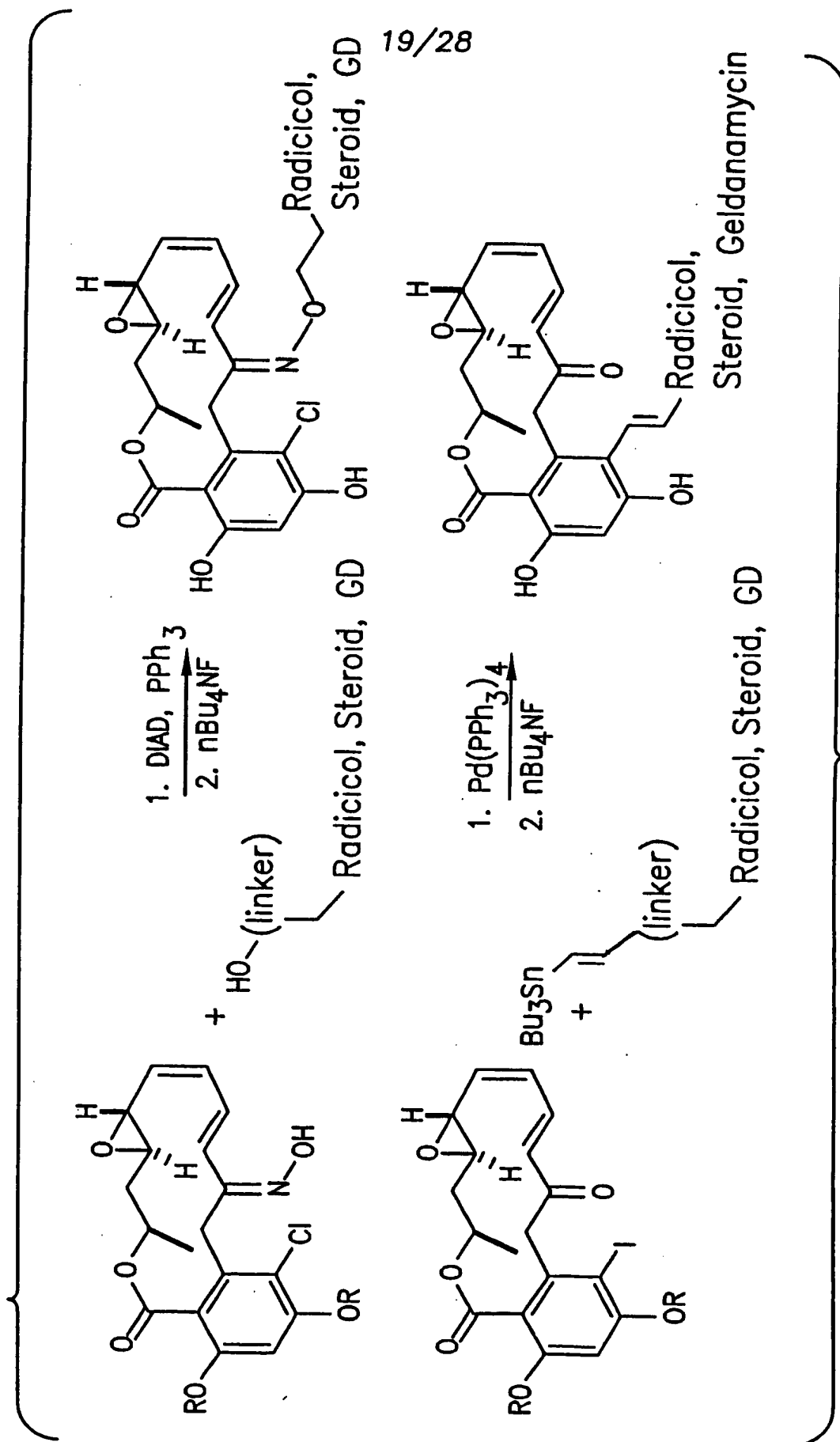


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GD=Geldanamycin

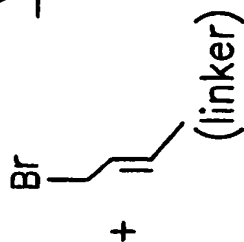
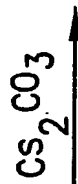
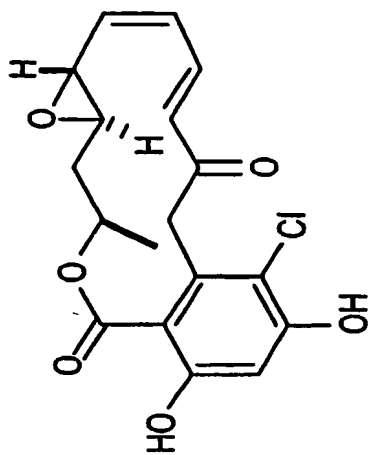
FIG. 16-1



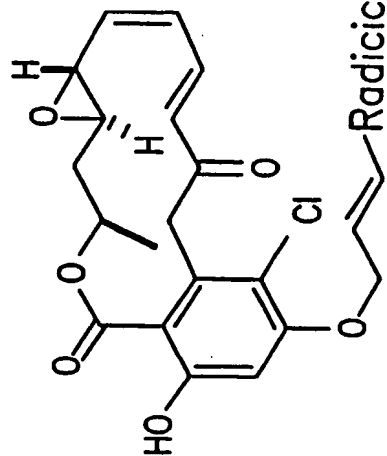
TO FIG. 16-2

FROM FIG. 16-1

FIG. 16-2



Radicalol, Steroid, GD

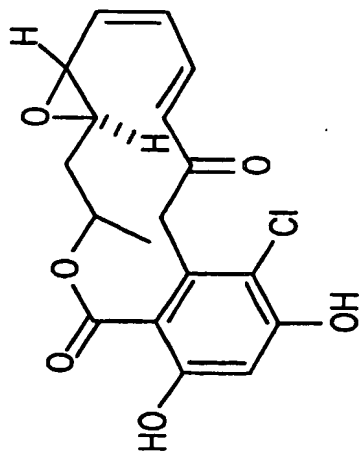


Radicalol, Steroid, GD

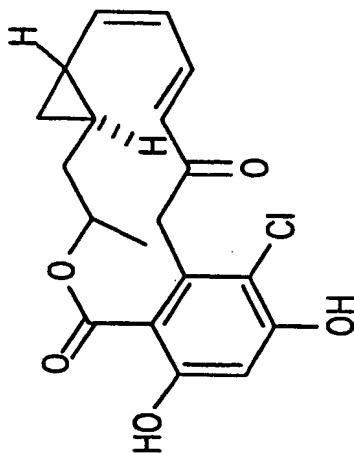
FIG. 17-1

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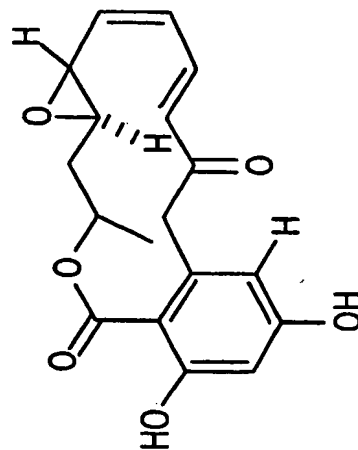
I. Radical



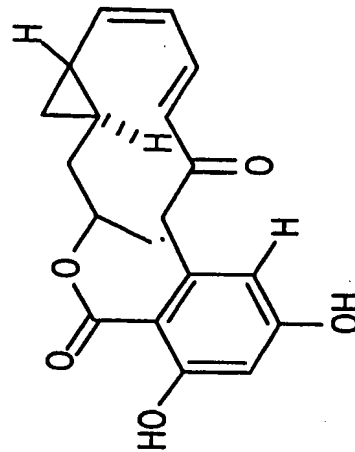
III. Cyclopropyl radical



II. Monocillin I



IV. Cyclopropyl monocillin

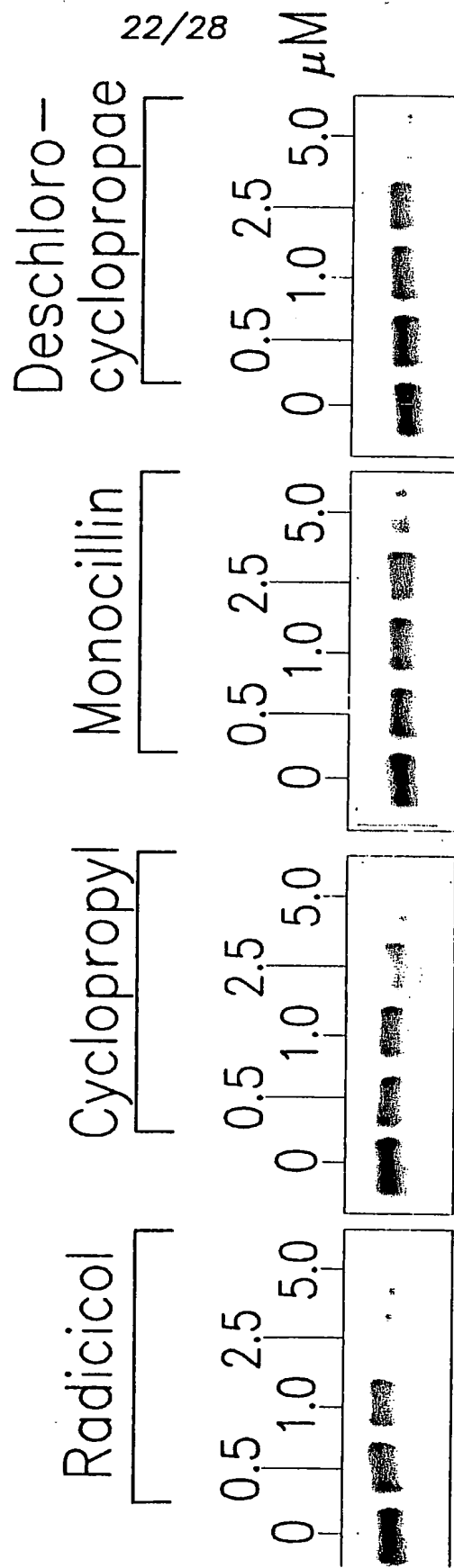


TO FIG. 17-2

FROM FIG. 17-1

## FIG. 17-2

*MCF7 Cells Treated with Radicicol and Analogues*



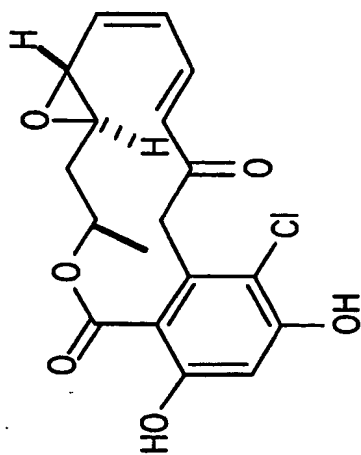
HER2

TO FIG. 17-3

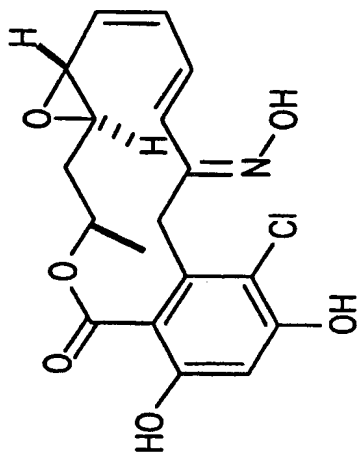
FROM FIG. 17-2

## FIG. 17-3

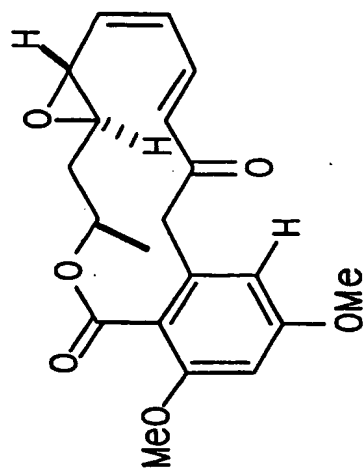
I. Radical



VII. Radical Oxime



V. Dimethyl Monocillin I



VI. Dimethyl Radical

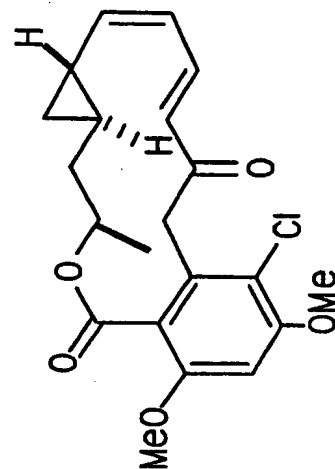
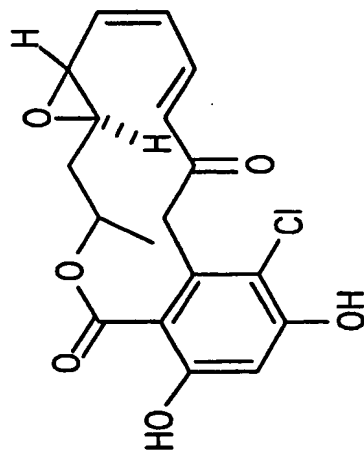




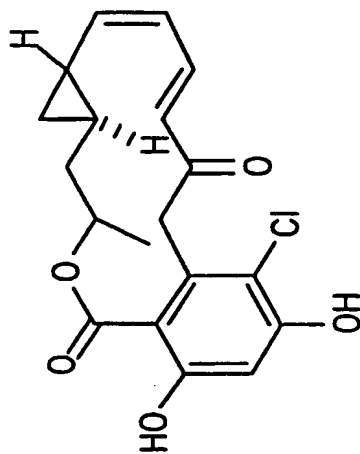
FIG. 18-1

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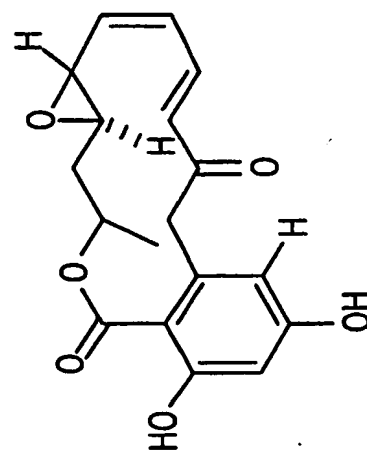
I. Radicol



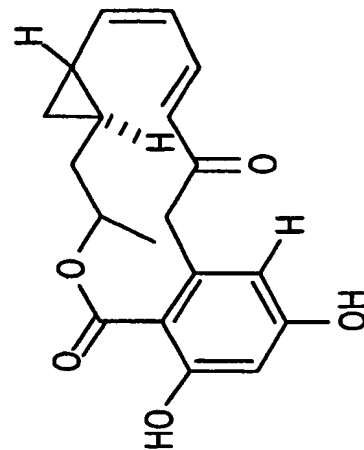
III. Cyclopropyl radicol



II. Monocillin I



IV. Cyclopropyl monocillin



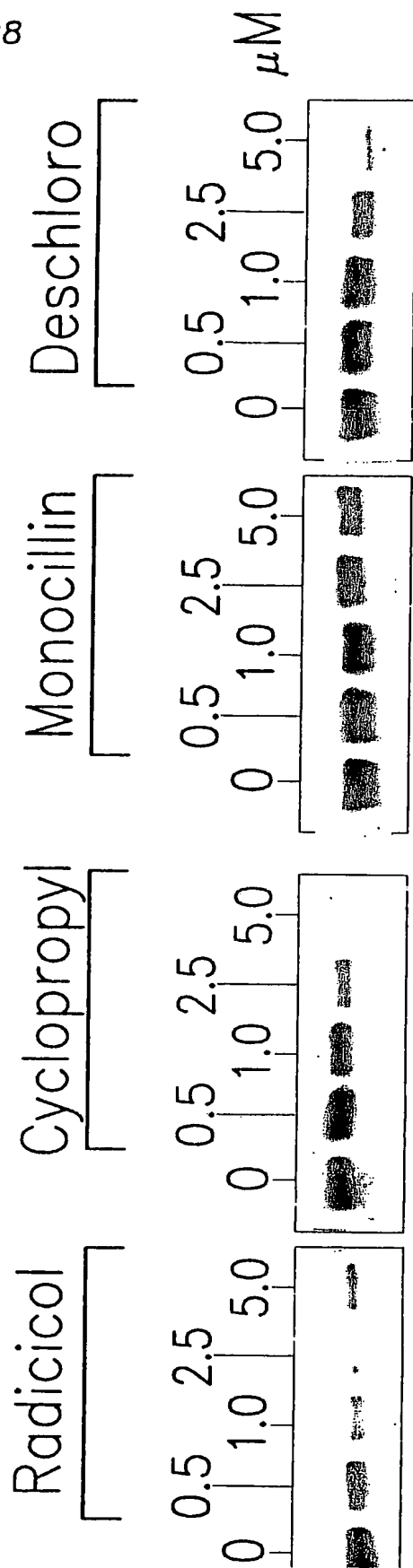
TO FIG. 18-2

FROM FIG. 18-1

## FIG. 18-2

BT474 Cells Treated with Novel Radicicoliols (24hrs.)

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HER2

FIG.19

Growth of MCF7 Treated with Radicicol and Derivatives of Radicicol

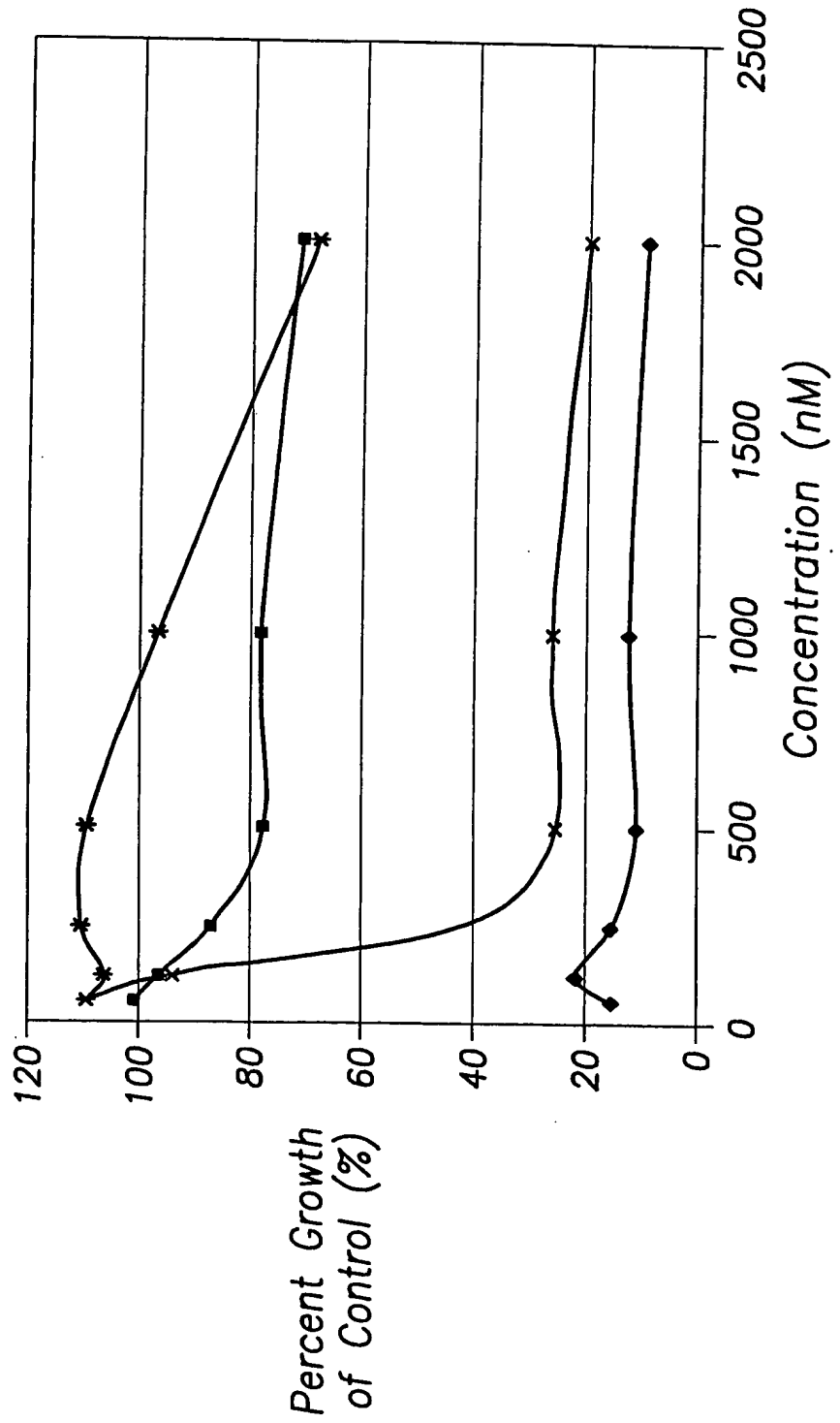


FIG.20

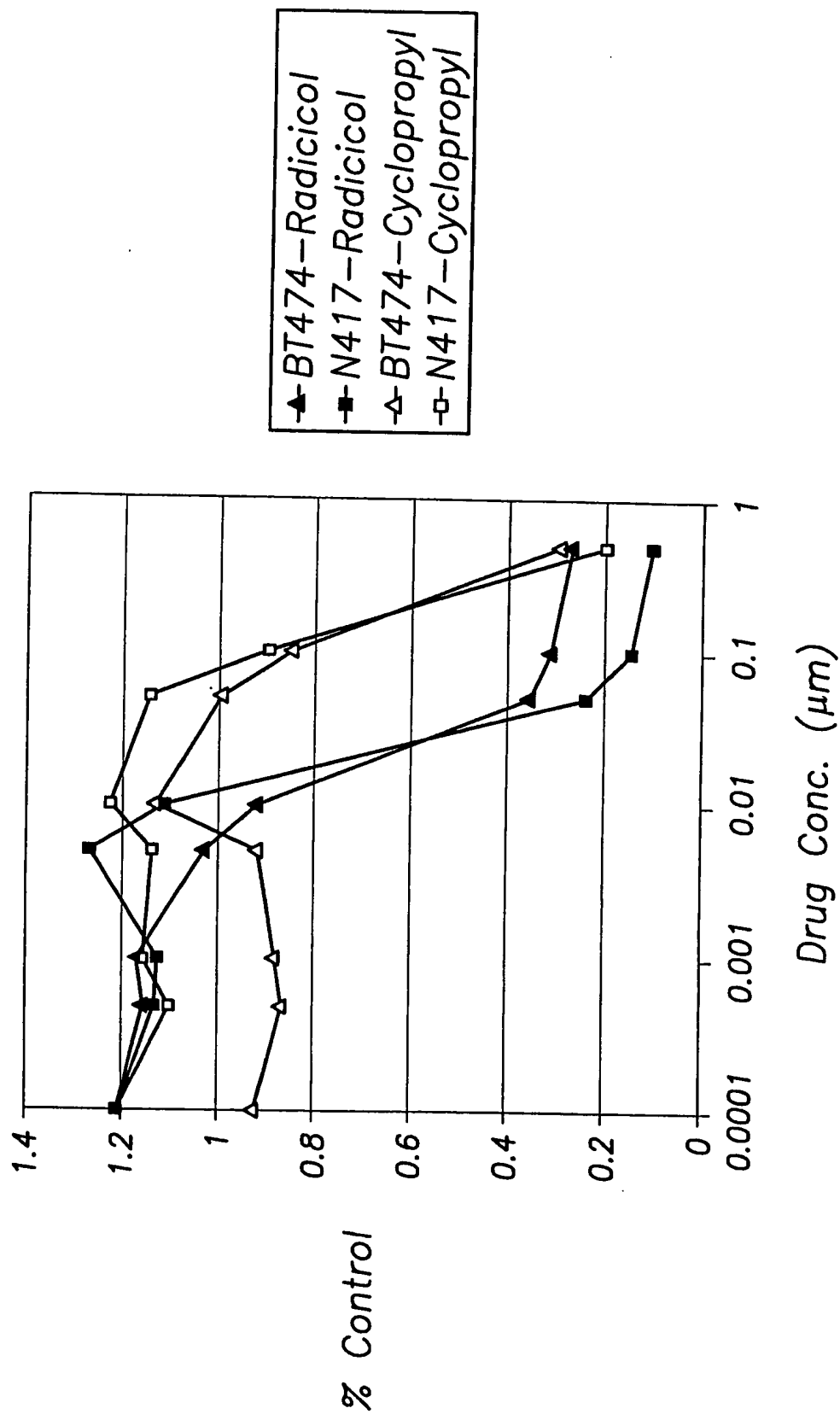
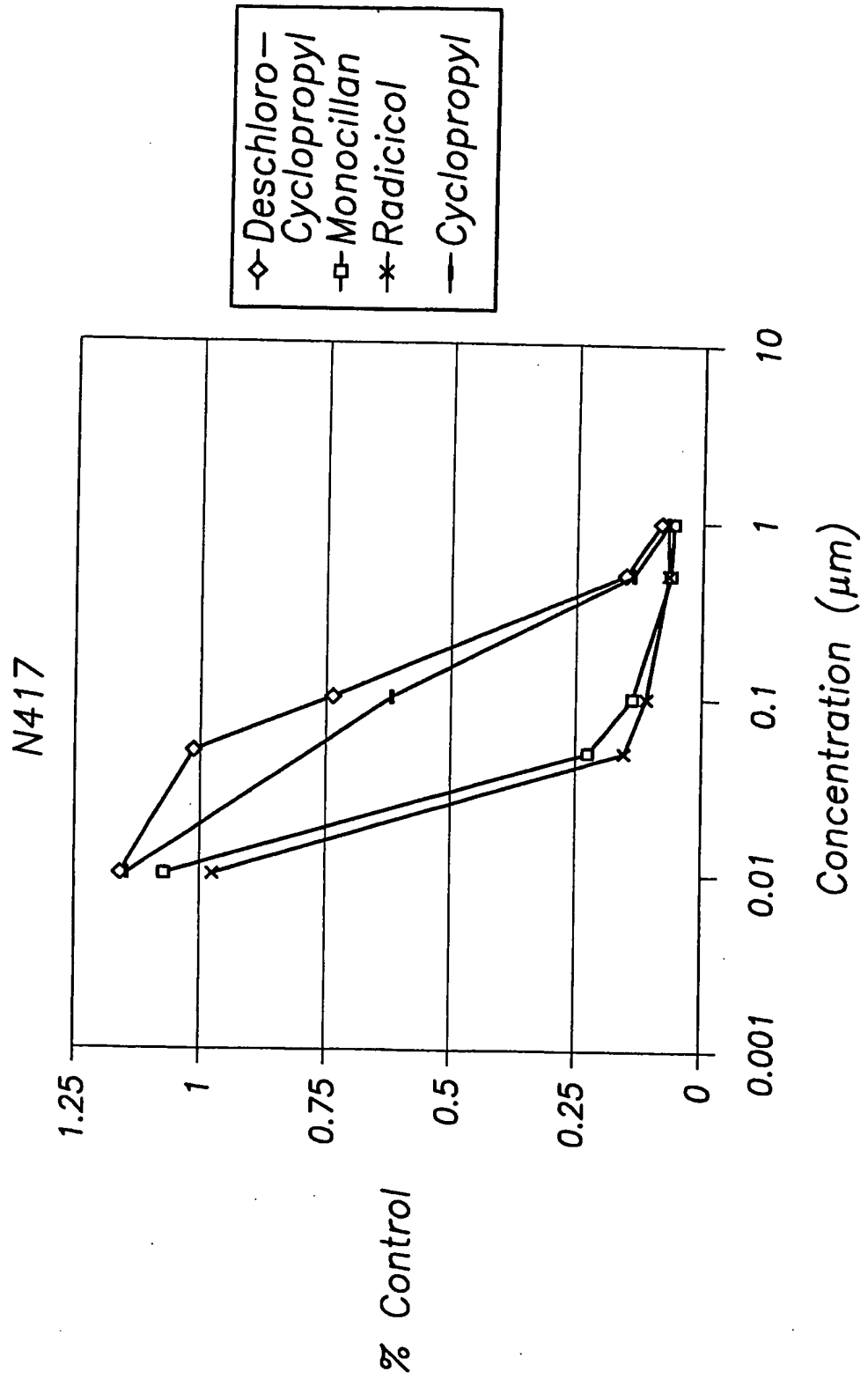


FIG. 21



Therapeutic Effect of Cycloproparadicol in Nude Mice Bearing Human Mammary Carcinoma MX-1 Xenograft (Q2Dx7, iv.injection)

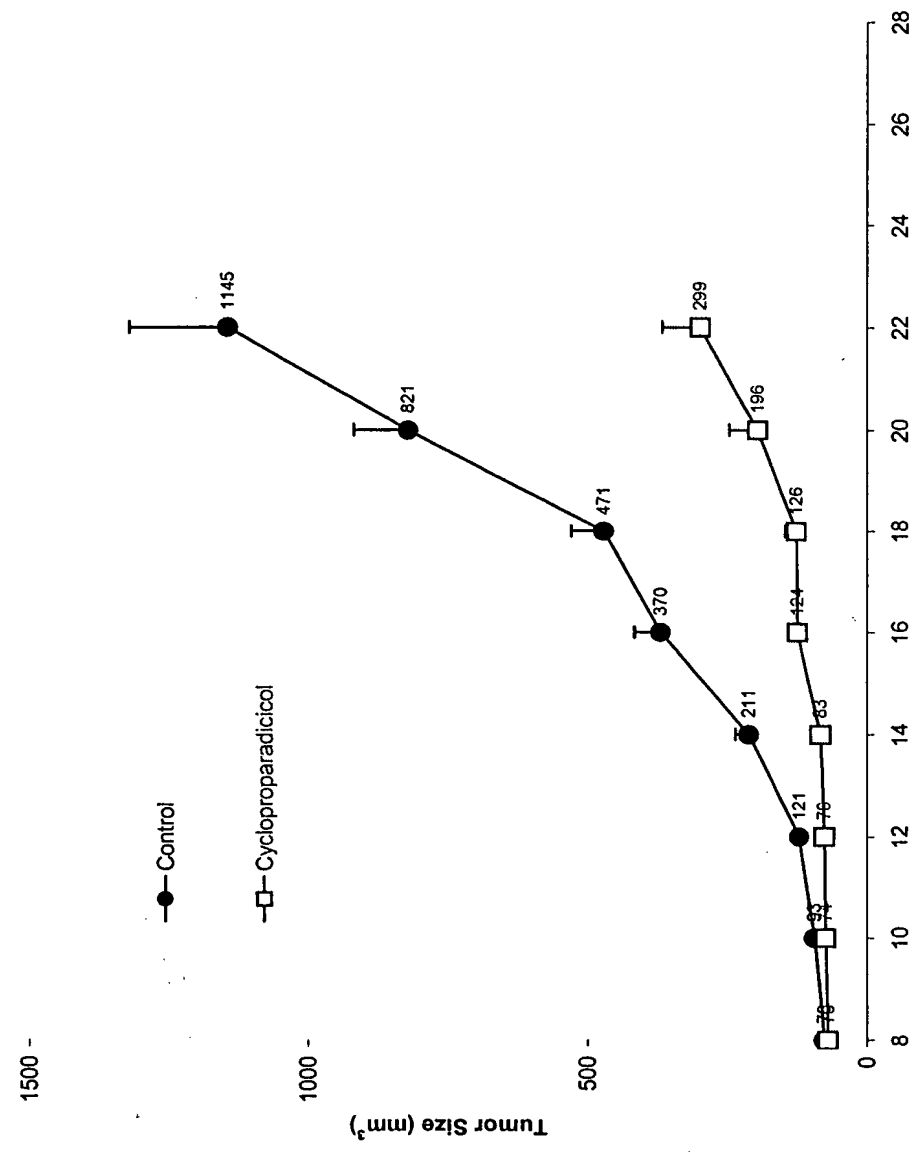


FIG. 22

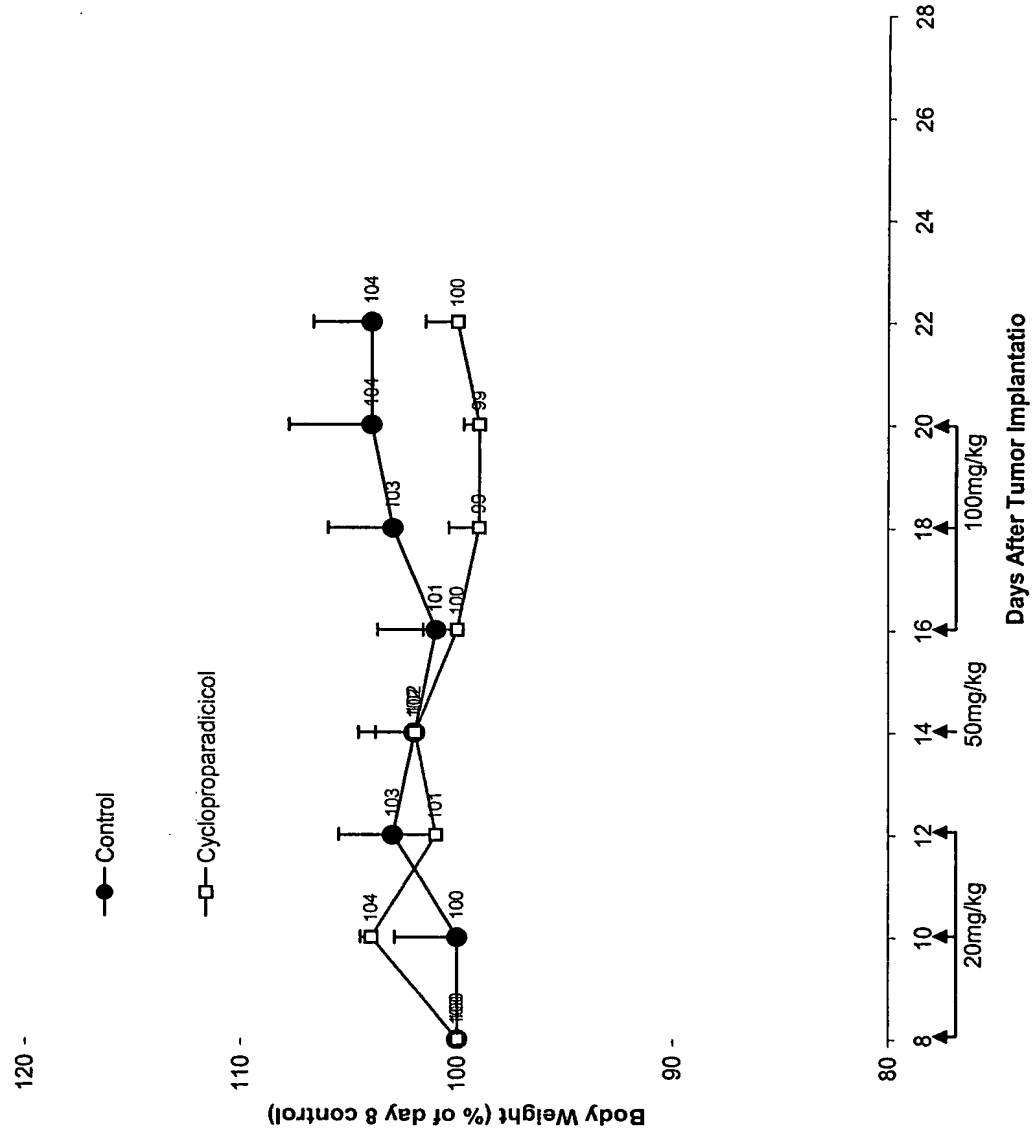
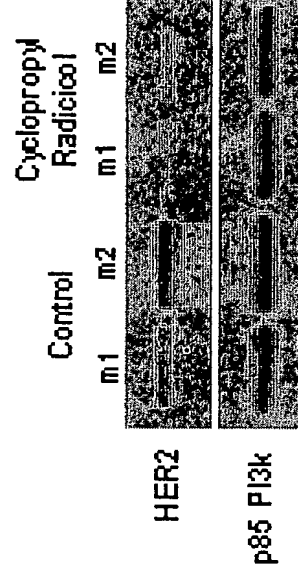


FIG. 23

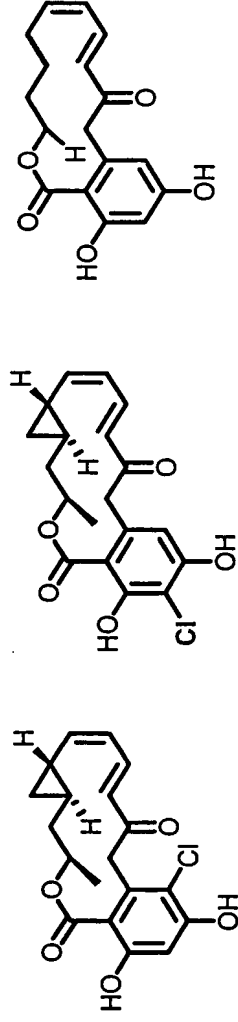
**MX-1 tumors**  
**12 hrs following a 6 hr CIVI**



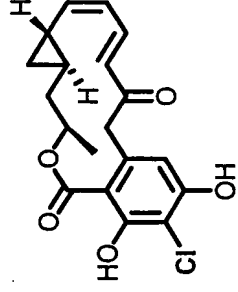
**FIG. 24**



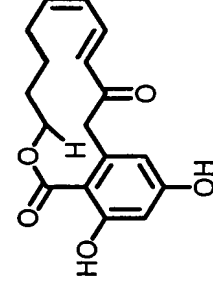
# IC<sub>50</sub> of Growth Inhibition of Different Tumor Cell lines



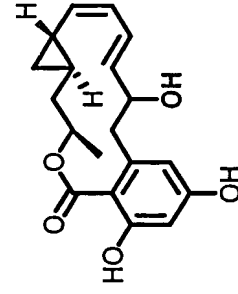
Cell lines  
MCF-7 54 nM  
CCRF-CEM 42 nM  
CCRF-CEM/Vinblastin resistant 32 nM



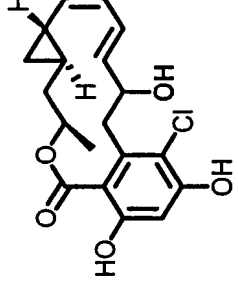
>500 nM



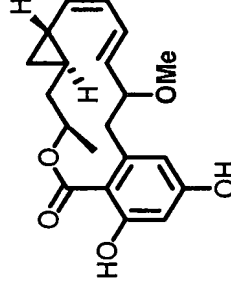
>500 nM



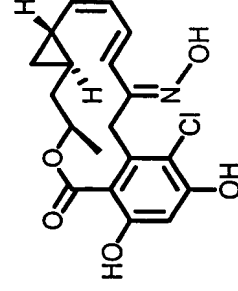
Cell lines  
MCF-7 150 nM, >500 nM  
CCRF-CEM 208 nM  
CCRF-CEM/Vinblastin resistant 209 nM



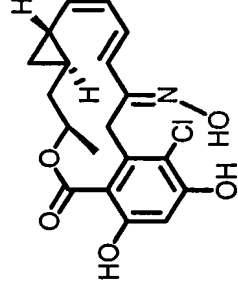
390 nM



>500 nM  
>5 μM



98 nM



282 nM

Cell lines  
MCF-7

FIG. 25

# Degradation of HER2 by Cycloproparadicol Analogues

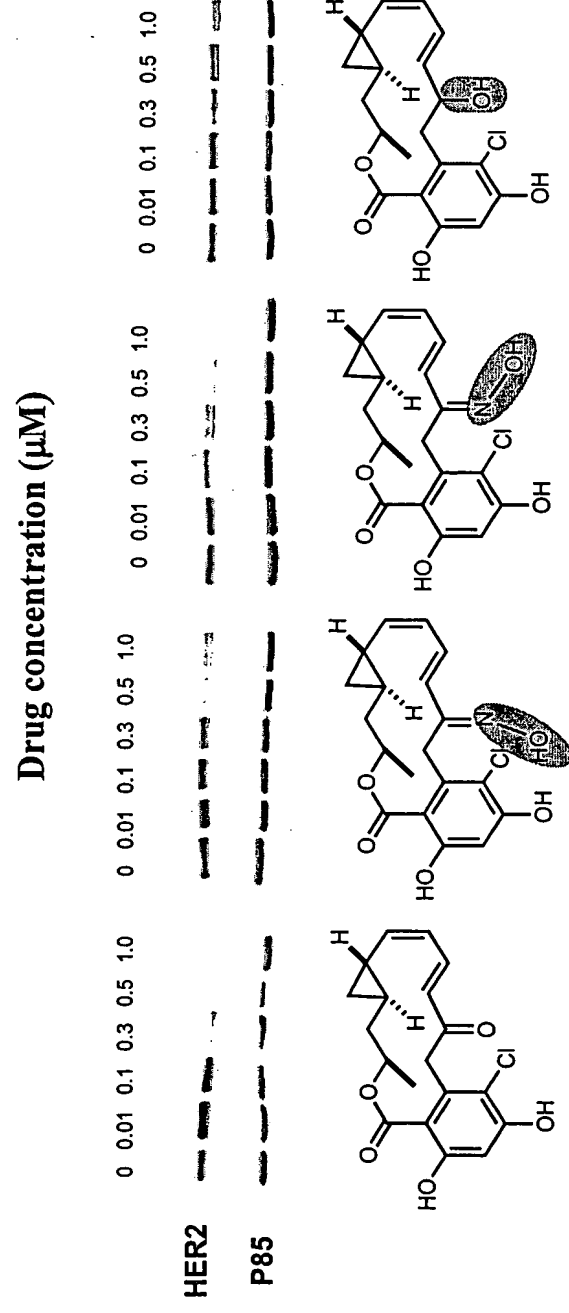


FIG. 26

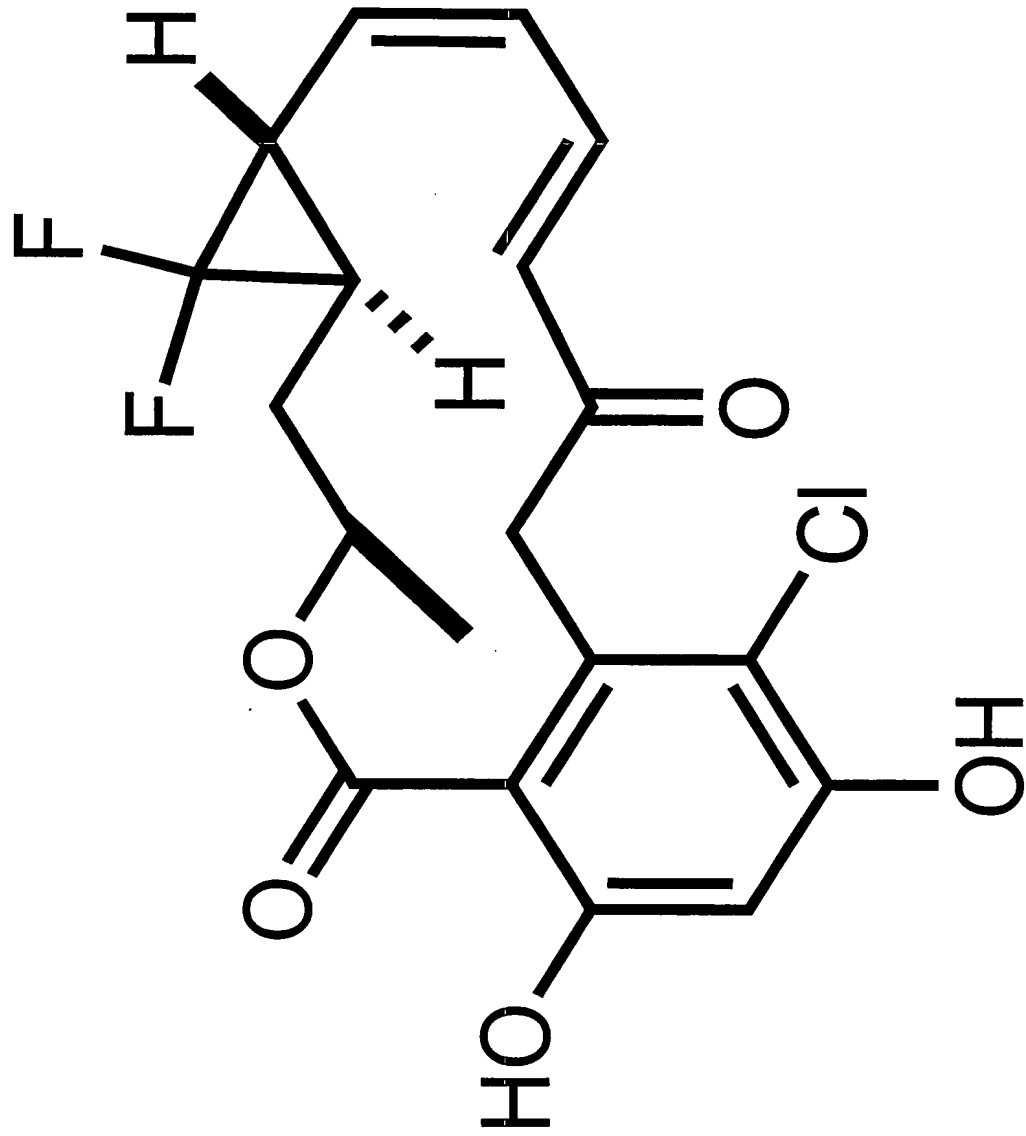


FIG. 27